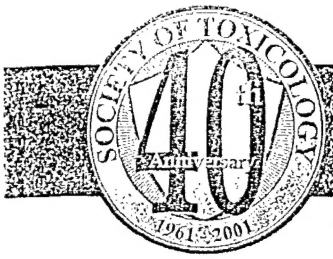

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(15 mg/kg) that was without effects in saline-treated animals produced a 60% reduction of motor activity in PQ exposed mice. In 5 month and 18 month old mice treated with PQ alone (2x/week for 3 weeks), decreases in locomotor activity and motor coordination were detected and these effects were age-dependent. Striatal tyrosine hydroxylase (TH) activity was enhanced by approximately 30% in 5 month but not in 18 month old mice injected with PQ. Three months following the last PQ dose, an 18% decrease in striatal TH protein levels was observed only in 18 month old mice. Taken together, these data suggest that the neurotoxic effects of PQ are both age-dependent and progressive. ES01247, ES10791 and ES10806.

1132 PARAQUAT (PQ)-INDUCED DOPAMINERGIC (DA) CELL LOSS IN THE MOUSE *SUBSTANTIA NIGRA*.

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Epidemiological and experimental evidence suggests a role of pesticides and, in particular, PQ as risk factors for human Parkinsonism. The goal of this study, using a state-of-the-art stereological technique, was to determine whether PQ exposure could reduce the number of DA neurons in the substantia nigra of mice, a pathological hallmark of Parkinson's disease (PD). C57BL/6 mice 8 weeks of age were exposed to two regimens of PQ administration. Under the subchronic treatment, mice were injected intraperitoneally with 0, 1, 5 or 10 mg/kg PQ once a week for three consecutive weeks. The second or acute regimen consisted of a single intraperitoneal injection of 0, 10 or 30 mg/kg PQ. Mice were sacrificed three days after the last (subchronic treatment) or the single (acute regimen) PQ exposure, the midbrain was fixed and cut into coronal slices, and slices were processed for both Nissl staining and tyrosine hydroxylase immunocytochemistry. PQ produced a dose-dependent loss of nigral dopaminergic neurons in subchronically-treated animals. The number of neurons was reduced by approximately 10%, 20% and 35% in mice injected with 1, 5 and 10 mg/kg PQ, respectively. No cell loss was seen after a single administration of 10 mg/kg PQ, while a 30% decrease in dopaminergic neurons was induced by the acute 30 mg/kg regimen. Taken together, these data strongly support a neurotoxic role of PQ and warrant further investigations of its potential involvement in nigrostriatal degeneration in PD. They also underscore the critical role of protracted exposure in PQ neurotoxicity. ES01247, ES10791 and ES10806.

1133 AGE-RELATED AND IRREVERSIBLE NIGROSTRIATAL DOPAMINE (DA) SYSTEM NEUROTOXICITY OF COMBINED EXPOSURE TO PARAQUAT (PQ) AND MANEB (MB).

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Combined exposures of young adult mice to the herbicide PQ and the fungicide MB results in potentiated toxic effects that target the nigrostriatal DA system (the same system that is affected in Parkinson's disease (PD)). Since, in addition to environmental and genetic factors, normal aging is a risk factor for PD, this study hypothesized enhanced sensitivity to these treatments with advancing age. C57BL/6 mice of 6 weeks, 5 months or 18 months of age were treated 2X/week for 3 weeks with saline, 10 mg/kg PQ, 30 mg/kg MB or PQ+MB. Decreases in locomotor activity and motor coordination (beam walk and inverted screen measures) were age-dependent, with the 18-month PQ+MB mice being most effected. Similarly, failure to evidence recovery of locomotor activity 24 hr post-injection was most pronounced in the 18 month PQ+MB group. DOPAC and DA turnover were also furthest reduced in the 18 month PQ+MB group 10 days post treatment. Measurement of tyrosine hydroxylase (TH) enzyme activity indicated that 5 month, but not 18 month old mice were able to compensate for striatal TH and/or DA loss following PQ+MB treatment as TH activity was increased in the former group, but decreased in the latter. Three months post-treatment, only the 5 and 18 month PQ+MB groups evidenced residual reductions of locomotor activity and motor coordination. Furthermore, striatal TH protein levels of both of these groups remained 40% below control values. Stereological assessment of potential DA cell loss is currently underway. Collectively, these data confirm enhanced sensitivity to the nigrostriatal neurotoxicity of PQ+MB with age and that the effects of these exposures are irreversible. These chemical mixtures may be environmental risk factors for PD. The potentiated nature of PQ + MB effects also raise questions about current risk assessment paradigms. ES01247, ES10791 and ES10806.

1134 COMBINED EXPOSURE TO PYRIDOSTIGMINE BROMIDE (PB), DEET, AND PERMETHRIN WITH STRESS INCREASES BLOOD-BRAIN BARRIER (BBB) PERMEABILITY AND INHIBITS BRAIN ACETYLCHOLINESTERASE IN RATS.

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Two groups of 15 male Sprague-Dawley rats weighing 225-250 g, were administered PB (1.3mg/kg/d, oral), DEET (40mg/kg/d, dermal), and permethrin (0.13mg/kg/d, dermal) for 28 days. Animals in one group were stressed by placing them in a Plexiglas® restraint tube for 5 mins. each day for the duration of the experiment. A third group of 15 animals were treated with similar treatment with stress and vehicle but no chemical and fourth group of 15 animals received only saline and ethanol and served as controls. Three sets of five animals from each group were processed for: 1) BBB permeability studies by injecting [^{3}H]hexamethonium iodide; 2) i.v. injection of 2mg 10% type IV horseradish peroxidase (HRP) in saline; 3) biochemical assay for acetylcholinesterase (AChE) and m2 muscarinic receptor. Both stress and chemical treatment alone caused an increase in BBB permeability; however the chemical and stress combination caused even greater increase in BBB permeability. AChE activity was inhibited by a combination of chemical and stress treatment. M2 muscarinic receptor ligand binding density was decreased by treatment with chemical and stress in midbrain and cerebellum. HRP staining revealed focal perivascular accumulation of the stain in cerebral cortex, white matter, deep gray matter and brainstem in the animals treated with chemical and stress. These results indicate that combined exposure of chemicals and stress produced changes in the BBB permeability that may cause neurologic deficits. Supported, in part by the U.S. Army Medical research and Materiel Command under contract # DAMD 17-99-1-9020. The views, opinion and/or findings contained in this report are those of the authors and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

1135 STRIATAL DOPAMINERGIC PATHWAYS AS TARGETS OF CHLORPYRIFOS OR PERMETHRIN EXPOSURES: COMPARISON WITH THE PARKINSONIAN NEUROTOXIN MPTP.

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Male C57BL/6 mice from retired breeder stock were dosed for 2 weeks with permethrin (3 i.p. injections at 0.2-200 mg/kg) or chlorpyrifos (3 s.c. injections at 1.5-100 mg/kg). [^{3}H]Dopamine uptake was significantly increased at lower chlorpyrifos doses, peaking at 108% of control, while higher doses (100 mg/kg) of chlorpyrifos significantly repressed [^{3}H]dopamine uptake to 89% of controls. Dopamine uptake was also affected in a dose-dependent manner by permethrin treatment, resulting in a bell-shaped curve. At a dose of 1.5 mg/kg, dopamine uptake peaked at 125% of control, and declined at higher doses to 45% of control at 200 mg/kg. Immunocytochemical labeling of the striatum showed the level of transporter staining to be near that of controls. Further, there was no difference in [^{3}H]GBR 12,935 binding between the control and 200 mg/kg permethrin treatment groups. Therefore, decreases in dopamine uptake at high doses of insecticide may be due to toxic effects. Permethrin at a dose of 200 mg/kg significantly decreased mitochondrial dehyrogenase activity compared to controls. Striatal dopamine levels were not affected by treatment with either 100 mg/kg chlorpyrifos or 200 mg/kg permethrin; however, a dose of 100 mg/kg chlorpyrifos significantly increased striatal titers of the dopamine metabolite 3,4-dihydroxyphenylacetic acid (DOPAC). Permethrin at a dose of 200 mg/kg did not change DOPAC levels. Additionally, permethrin or chlorpyriphos dosed in conjunction with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) significantly decreased striatial dopamine levels as compared to controls and MPTP alone. These findings suggest that dopaminergic neurotransmission may be affected by exposure to permenthrin and chlorpyrifos and may contribute to the spectrum of toxicity elicited by these insecticides, including parkinsonism.